Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a novel inflammatory central nervous system disorder. The diagnosis is made on the basis of the radiological, neurological, neuropathological data and responsiveness to steroids treatment. The aim of this paper is to present a neuropsychological characteristic of cognitive, executive and linguistic symptoms characteristic for patient with CLIPPERS disease.

In this paper we present the case of a 42-year-old woman with hyperintense punctate foci in the pons, cerebellum, midbrain, thalamus, white matter of occipital lobes, with a short-term verbal memory deficits, mild deficiency in verbal and procedural learning, executive dysfunctions, hand-eye coordination impairment, psychomotor speed disabilities and dystarthria, associated with a chronic lymphocytic inflammation.

In this challenging diagnosis of CLIPPERS, neuropsychological analysis of cognitive functions can be important to optimize the diagnosis and treatment.

**Key words:** CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, cognitive disorders, neuropsychological assessment

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BACKGROUND

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a rare inflammatory central nervous system disorder, of still unclear pathology. CLIPPERS syndrome was first described in 2010 by Pittock in eight patients presented a brainstem-predominant inflammatory disease with predilection for the midbrain (Pittock et al., 2010). In relation to the constellation of neurological, radiological and histopathological features with significant clinical and radiological response to glucocorticosteroid treatment, the authors described this disease as a distinct form of brain encephalitis. Since that time, there has been reported more than 50 patients with CLIPPERS worldwide (Bladowska, Waliszewska-Prośól, Rojek, 2017). The limited number of such cases caused the lack of neuropsychological analysis of the cognitive functioning of the patients. This challenging diagnosis is made on the basis of the radiological, neurological, neuropathological data, exclusion of alternative diagnoses and responsiveness to steroids treatment.

The purpose of this paper is to present a neuropsychological characteristic of cognitive, executive and linguistic symptoms of patient with CLIPPERS disease, that we think can optimize the diagnosis and treatment.

CASE STUDY

A 42-year-old woman, right-handed, with a college education, suffered from imbalance, gait disturbances, vertigo, diplopia, facial tingling, tingling on the tongue, soft palate, cheeks and lips, altered sensation of the hands, feet and buttocks and memory problems since 3 months. Clinical neurological examination showed bilateral cerebellar ataxia with predominance on the left side and bilaterally increased deep tendon reflexes. Electroencephalogram, standard and more specific blood tests and the cerebrospinal fluid analysis reveal no significant abnormalities. A brain magnetic resonance imaging (MRI) with gadolinium showed the presence of hyperintense punctate foci in the pons, midbrain, cerebellum, right thalamus, white matter of occipital lobes and a small foci in white matter of both hemispheres (Fig. 1).

Fig. 1. The initial brain MRI: T1-weighted post-Gadolinium axial scan (A-C), T2-weighted sagittal scan (D)
MRI of the cervical spine was normal. The initial treatment was the methylprednisolone in the dose of 1g over 5 days intravenously, followed by oral glucocorticosteroid. A control brain MRI performed after 6 months showed significant regression of changes (Fig. 2).

Mental state
The patient maintained logical, spontaneous verbal contact. Her utterances were fluent, factual, adequate to given questions and rich in information. Orientation to time, place and person was preserved. The patient was fully self-aware of her situation. The psychomotor drive was significantly slowed. The psychological diagnosis showed high emotional tension, impaired adaptability and low tolerance of stressful situations. She suffered from general anxiety disorders with breathing disorders (breathing corset), sleep disturbances, lack of appetite. The patient heightened her fear in closed space (claustrophobia).

Memory and learning
Activities assessing the memory and learning processes demonstrated abnormalities in coding and obtaining information. The California Verbal Learning Test (CVLT) demonstrated low results of direct recollection, flat learning curve with dominating recency effect in spontaneously recalling (Table 1). Many perseveration and intrusion errors were observed in learning process. The information were permanently consolidated in long term memory, but the patient experienced moderated problems with recall the previously remembered words. In everyday activity she had difficulties in immediate recall of necessary facts, she reconstructed them with delay, which indicated executive deficits. The patient had also procedural memory problems.

The neuropsychological examination performed 6 months after the steroids treatment showed improvement in terms of efficiency of concentration, durability and spillness of attention. The capacity of verbal direct memory were slightly

Fig. 2. The follow-up brain MRI: T1-weighted post-Gadolinium axial scan (A-B), T2-weighted sagittal scan (C)
below standard. The California Verbal Learning Test (CVLT) showed persistent mild difficulties in learning. Disorders of direct memory were on the same level, below expectations. The learning curve was quite flat, with a few perseveration errors, but the primacy and recency effect was properly marked. The patient used strategy of words categorization in semantic groups to a limited extent, based on less effective learning strategy consisting of recalling words in order of hearing. After long-term delay, the patient was able to spontaneously recall 10 of previously remembered words. Additionally, an improvement was observed in the tests of recognition, compared to the state before treatment.

**Executive functions**

The assessment of executive functions performed during the initial period of illness showed the largest deficits (Frontal Assessment Battery FAB=13 out of 18 points). She scored low in tests assessing cognitive flexibility (Table 2). Besides of recalling information, there was difficulty with planning. The patient had severe problems with plan of solving the Tower of Hanoi Test. A tasks showed many unnecessary movements. There were also problems with planning movement sequences.

After the steroids implementation executive functions examination showed improvement (FAB=17 out of 18 points). Despite of normal global range, during the neuropsychological observation, slight deficits in planning and searching of semantic resources were observed, but less severity than before treatment. Definite improvement was observed in planning movement sequences.

### Table 1. The memory and learning assessment

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Results (before treatment)</th>
<th>Results (6 months after treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (1-5)</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td>Learning curve</td>
<td>5-8-10-10-10</td>
<td>5-10-10-13-14</td>
</tr>
<tr>
<td>Perseverative errors</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Intrusion errors</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Short-term delayed recall</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Long-term delayed recall</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Recognition</td>
<td>13; 3 confabulations</td>
<td>14</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copy</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>3-minute delay</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Digit span:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Backward</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Trial Making Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>66 s</td>
<td>32 s</td>
</tr>
<tr>
<td>Part B</td>
<td>89 s</td>
<td>61 s</td>
</tr>
<tr>
<td>B-A</td>
<td>23</td>
<td>29</td>
</tr>
</tbody>
</table>
Linguistic functions

One of the symptoms of patient's disease was articulation impairment – mixed dysarthria. A segmental and suprasegmental deficits were observed. There were distortion in relation to implementation of sounds that needed exact coordination and increased muscle tension within articulation organs. Coordination disorders appear while speaking, although isolated movements were relatively correct. Weakened feeling on the face, especially lips and around circular muscle of the mouth lead to incorrect implementation of labial (p,b,w,f). The patient also felt numbness of the muscles of the tongue, what caused difficulties in realization of pre-linguistic consonants (t,d,r,s). Incorrect articulation included also palatal consonants (g,k). Elisions and deformations of sounds appeared during speaking.

Six months after the treatment implementation articulation improvement was observed, though patient still paid attention to little weakened feeling on the lips and around circular muscle of the mouth.

Visual-spatial functions

Searching the visual field was slowed down, but after treatment it became more efficient. Visual gnosis in the aspect of real world object recognition, object drawings including incomplete, masked or overlapping pictures and visual-spatial functions within perception of spatial relations between elements remained intact.
Visual-motor coordination

One of the symptoms was severe impairment of visual-motor coordination. Disorders of psychomotor speed and fast, precise, smooth movements, turned into difficulties with professional work responsibilities and the patient was forced to change her workplace.

After steroids treatment psychomotor speed and visual-motor coordination were improved.

Sensory functioning

The sensory dysfunctions were diagnosed. The patient suffer from hiperosmia, hyperacusis and diplopa. After steroids treatment hypersensitive to sounds decreased and to scents was in a complete remission. Visual perception was also improved.

DISCUSSION

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a novel, treatable inflammatory central nervous system (CNS) disorder, involving the brainstem, particularly the pons, but lesions may additionally include cerebellum, spinal cord, thalamus, basal ganglia, capsula interna, corpus callosum and white matter (Dudesek et al., 2014). Including the lymphocytic predominant CNS inflammation and the clinical and radiological responsiveness to immunosuppression with glucocorticosteroids, CLIPPERS has been considered as an immune-mediated, inflammatory process of uncharted aetiology. This newly described, rare disease can occur at any age, ranging from 16 to 86 years and affects both genders with a minor male predominance.

The key features of CLIPPERS are related to brainstem, cranial nerve or cerebellar dysfunctions. Prominent symptoms, which may present in various combinations, include: gait ataxia, dysarthria, dysphagia, diploia, altered sensation or tingling of the face, vertigo, hyperacusis, hearing impairment. Additional features can referable to long tract affections or spinal cord syndrome (e.g. para/tetraparesis, spasticity, deep sensation), pseudobulbar affect (pathological crying or laughter), headaches and abnormal fatigue (Tobin et al., 2017). In some patients descriptions of clinical manifestation of CLIPPERS include also cognitive dysfunctions, e.g. mnestic deficits, dysexecutive syndrome, psychomotor slowing (Simon, 2012; Kastrup, 2011). The limited number of such cases caused the lack of neuropsychological analysis of the cognitive symptoms. The diagnosis is made on the basis of the radiological, neurological, neuropathological data and responsiveness to steroids treatment.

In this paper we presented a case report including the neuropsychological characteristic of cognitive, executive and linguistic symptoms of a 42-year-old female patient with CLIPPERS disease. In the neuropsychological examination of our patient the following cognitive symptoms were observed: short-term verbal memory deficits, mild deficiency in learning (low results of direct recollection, flat
learning curve with dominating recency effect, many perseveration and intrusion errors in learning process, moderate problems with recognition), procedural memory deficits, executive dysfunctions (recalling information, planning), slower pace of intellectual processes, attention disorders, hand-eye coordination impairment, psychomotor speed disabilities.

Our results, especially in the psychological diagnosis, which showed high emotional tension, impaired adaptability and low tolerance of stressful situations, as well as general anxiety disorders with breathing disorders (breathing corset), sleep disturbances, lack of appetite, might be interpreted by microgenetic theory. It should be stressed that the formation of the self system, including the sense of the self, in relation to full consciousness and meta-consciousness in microgenesis is illustrated in Fig. 3. Three main types of self can be distinguished here, after Pąchalska (2019):

1. **biological self** (primary, biological being, organism), which integrally connects with the structure and operation of the whole organism and its part (including the structure and neuronal connections of the brain) and consists in the fact that the subject feels and satisfies the drives and needs, which are literally egocentric. At this level there is no (and cannot exist) a so-called theory of mind, because it is not necessary for activities essential for survival;

2. **The emotional self** (feeling itself and the environment), which exists on the next, limbic level, connecting with the operation of the emotional system and manifests itself in emotional reactions. At this level, identity is associated with the subjectivity of a person experiencing pleasant or unpleasant emotions. Only then does the *I-You* relationship become possible, and hence, the beginning of the theory of mind. At the same level, the perception of the stimulus
is also separated from the body’s response to this stimulus. In other words, there is a separation of perception from action, with perception becoming the subject of the posterior parts of the brain, and action – more frontal lobes. This is due to complex cortico-cortical and cortico-subcortical connections (see also: Pačalska, Kaczmarek and Kropotov 2014). The feeling, experiencing the self of the limbic system becomes the central object of cognition in the world of objects that are analyzed according to specific, multimodal sensual and cognitive domains. Perceptual processes, in parallel with the processes of action, tend towards more and more precisely distinguishing the component of reality surrounding a given man.

3. The cognitive self (recognizing and being recognized) being the subject of one’s perception and action, connects with self-awareness and knowledge about oneself, self-sense, i.e., a subjective representation of oneself. Here, the identity is synthesized, thanks to which a person is born with a sense of identity, i.e., certainty that “I am myself” as both the object (being recognized Self) and the subject (recognizing Self) of perception. The self system - which is formed in the process of microgenesis – creates mutual relations and bonds between the biological self (primary, biological being, organism), the emotional self (feeling itself and the environment), the cognitive self (known and knowing) and self-awareness. Therefore, if these mutual relations and bonds between the biological self (primary, biological being, organism), the emotional self (feeling itself and the environment), the cognitive self (known and knowing) and self-awareness are disturbed because of the brain dysfunction in CLIPPERS disease, we can observe various disturbances presented by our patient.

CONCLUSIONS

Diagnosis of CLIPPERS is challenging, requires different specialist cooperation. Neuropsychological assessment of cognitive functions of the patient can be important to optimize the diagnosis and treatment.

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